(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 October 2005 (20.10.2005)

PCT

(10) International Publication Number
WO 2005/097747 A1

(51) International Patent Classification[7]: C07D 213/00, A61K 31/16, 31/165, 31/44

(21) International Application Number: PCT/US2005/011463

(22) International Filing Date: 5 April 2005 (05.04.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/559,715 5 April 2004 (05.04.2004) US

(71) Applicant *(for all designated States except US)*: **ATON PHARMA, INC.** [US/US]; 33 Avenue Louis Pasteur, Boston, MA 02115 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MILLER, Thomas, A.** [US/US]; 16 Garrison Road, #4, Brookline, MA 02445 (US). **WITTER, David, J.** [CA/US]; 3 Eagle Drive, Norfolk, MA 02056 (US). **BELVEDERE, Sandro** [IT/IT]; Corso Cavour 16, I-37121 Verona (IT).

(74) Agent: **ELRIFI, Ivor, R.**; Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Chrysler Center, 666 Third Avenue, New York, NY 10017 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HISTONE DEACETYLASE INHIBITOR PRODRUGS

(57) Abstract: The present invention is directed to prodrugs of hydroxamic acid based histone deacetylase (HDAC) inhibitors, e.g., suberoylanilide hydroxamic acid (SAHA). The prodrugs are acylated derivatives having increased aqueous solubility and cellular permeability as compared with the free hydroxamic acid, and are useful for inhibiting HDACs, and for selectively inducing terminal differentiation, cell growth arrest and/or apoptosis of neoplastic cells, thereby inhibiting proliferation of such cells. Thus, the prodrugs of the present invention are useful in treating a patient having a tumor characterized by proliferation of neoplastic cells. The prodrugs of the invention are also useful in the prevention and treatment of thioredoxin (TRX)-mediated diseases, such as autoimmune, allergic, and inflammatory diseases, and in the prevention and/or treatment of diseases of the central nervous system (CNS), such as neurodegenerative diseases.

WO 2005/097747 A1